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Review

Glucose-mediated cytoprotection in the gut epithelium under ischemic and hypoxic stress

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Summary. Single-layered intestinal epithelia play key roles in the maintenance of gut homeostasis and barrier integrity. Various types of epithelial cell death, including apoptosis, necrosis, and necroptosis, have been detected in ischemic and hypoxic stress conditions, thus resulting in bacterial translocation and gut-derived septic complications. Cytoprotective strategies, such as enteral glucose uptake, rescue intestinal epithelium from cell death after ischemic and hypoxic injury. Although glucose metabolism and energy production are generally considered to be the key factors in cytoprotection, the precise modes and sites of action have not been clarified. Our recent studies have demonstrated that energy restoration promotes crypt hyperplasia but does not prevent epithelial cell death under ischemic stress. On the other hand, glycolytic pyruvate prevents epithelial cells from undergoing apoptosis and necroptosis by scavenging free radicals in an ATP-independent manner. Distinct gut protective mechanisms involving ATP, pyruvate, glucose metabolic enzymes, and sodium-dependent glucose transporter activation are discussed here. Overall, glucose-mediated cytoprotection may be a universal mechanism that has evolved in epithelial cells for the maintenance of intestinal homeostasis. Enteral glucose supplementation is beneficial as a perioperative supportive therapy for the protection of gut barrier integrity.

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Histophysiology of intestinal epithelium

Intestinal epithelial cells undergo rapid turnover in a state of dynamic equilibrium and play a crucial role in maintaining homeostasis. Stem cells in the crypt divide and migrate upward and become differentiated epithelial cells with digestive, absorptive, and secretive functions. The fully differentiated cells develop a long brush border with extensive expression of membranous enzymes and transporters, which facilitate nutrient uptake. On the villus tip or surface extrusion zone, the epithelial cells are shed and undergo apoptosis (Yen and Wright, 2006; Yu et al., 2012). Although surface cell apoptosis occurs, an intact epithelial barrier is sustained under physiological conditions (Madara, 1990; Guan et al., 2011).

Because they serve as a portal to the external environment, epithelial cells are often exposed to noxious agents and infectious pathogens. High levels of commensal bacteria are also present in the gut lumen. A favorable symbiotic relationship between the host and microbes is dependent on the integrity of the single-layered epithelial barrier (Ley et al., 2006; Yu et al., 2012). With a dynamic turnover rate of 5-7 days, cytoprotective mechanisms evolved by epithelial cells represent the basis of gut homeostasis. A number of cytoprotective mechanisms have been proposed, including nutrient uptake and transcriptional adaptation.

Glucose transport and metabolism in intestinal epithelial cells

Glucose transporters are ubiquitously expressed on all cell types in the body, including three subtypes of sodium-dependent glucose transporters (SGLTs) and fourteen members of glucose transporters (GLUTs). In the small intestinal epithelial cells (enterocytes), the major transporter expressed on the apical membrane for active glucose uptake is SGLT1, whereas GLUT2 is responsible for the basolateral diffusion of glucose into the bloodstream (Ferraris and Diamond, 1997; Daniel and Zietek, 2015). Glucose binding to SGLT1 activates downstream signaling for insertion of GLUT2 into the apical membrane for facilitative diffusion of enteral glucose (Kellett and Helliwell, 2000; Mace et al., 2007). Aside from glucose transport, enterocytes also express apical GLUT5 for uptake of dietary fructose (Ferraris and Diamond, 1997). On the other hand, large intestinal epithelial cells (colonocytes) do not normally express SGLT1 or GLUT2 but are equipped with GLUT5 and GLUT6 (Godoy et al., 2006).

The metabolic pathways in enterocytes and colonocytes are different. Preferential energy sources for enterocytes include glucose and glutamine; the former predominantly undergoes anaerobic glycolysis, and the latter predominantly undergoes mitochondrial respiration for energy production (Kight and Fleming, 1995; Fleming et al., 1997). Owing to the presence of anaerobic bacteria in the large intestine, short chain fatty acids (e.g., butyrate) fermented from dietary fiber after diffusion through the lipid bilayer membrane are the major energy source for colonocytes (Roediger, 1982; Wong et al., 2006). The utilization of butyrate for mitochondrial oxidative phosphorylation in colonocytes generates more than half of the energy output, even in the presence of glucose (Roediger, 1982; Wong et al., 2006).

Intestinal absorption of glucose is remarkably adaptive, and the uptake level changes according to diet, age, energetics, and stress. After ingestion of dietary carbohydrate, glucose transporter expression on enterocytes is observed within minutes to several hours (Diamond and Karasov, 1987; Ferraris and Diamond, 1992). In contrast, total parenteral nutrition or fasting for a prolonged period may lead to decreased epithelial glucose uptake in the small intestine (Kotler et al., 1980). Hormones that regulate mucosal growth and transporter activity and consequently increase glucose uptake include gastrin, neurotensin, glucagon-like peptides, and epidermal growth factor (Ferraris and Diamond, 1997). Recent evidence has shown that luminal contents, such as the presence of glucose and non-metabolized sugars (such as artificial sweeteners), activate taste receptors and result in upregulation of the expression of SGLT1 (Moran et al., 2010; Stearns et al., 2010). In addition, bacterial lipopolysaccharide binding also stimulates translocation of intracellular vesicular SGLT1 to the apical membrane (Yu et al., 2006).

Cells that undergo hypoxic stress respond by adapting to increased glucose uptake. Previous studies have demonstrated transcriptional upregulation of GLUT-1 by binding of hypoxia-inducible factor (HIF)-1 to a hypoxia-responsive element in the promoter region of the glucose transporter (Ouiddir et al., 1999; Hayashi et al., 2004). A recent study has shown an increase in GLUT1 and GLUT4 transcript and protein levels of colonic epithelial cell lines after hypoxic challenge (Huang et al., 2013). Overall, the fluctuations of glucose transporter expression may reflect the fundamental metabolic requirements for cell survival.

Epithelial cell death and barrier damage in response to stress

Owing to the anatomical structure and vascular distribution, surface epithelia are the most fragile cell types in the gut tissues after exposure to ischemic and pathogenic stress. Surface cell death and mucosal ulceration are repaired by crypt hyperplasia through epithelial restitution and wound healing. Various types of epithelial cell death, including apoptosis, necrosis, and necroptosis, have been documented in the gut. Apoptosis and necroptosis are programmed cell death processes that are regulated by a cascade of signaling molecules. Apoptosis is characterized by caspase activation and DNA fragmentation. Necroptosis is executed by receptor-interacting protein (RIP)1/3 signaling and mitochondrial generation of reactive oxygen species (ROS), thus eventually resulting in necrotic features of the cells. In contrast, necrosis is an uncontrolled, unregulated form of cell death. Detailed information on the types of cell death, has been described in other articles (Vandenabeele et al., 2010; Gunther et al., 2013; Linkermann and Green, 2014; Huang and Yu, 2015).

Excessive epithelial cell death and gut barrier dysfunction have been observed after exposure to metabolic, inflammatory, oxidative, and heat stress. Metabolic stress in the gut is primarily caused by depletion of oxygen and nutrients, such as during mesenteric ischemia, trauma, hemorrhagic shock, necrotizing enterocolitis, and major abdominal and vascular surgery (Sreenarasimhaiah, 2005; Jilling et al., 2006; Zou et al., 2009; Yu, 2010; McElroy et al., 2013). An increase in apoptosis, necroptosis, and necrosis in gut epithelia has been observed in animal models of mesenteric ischemia/reperfusion (I/R) (Azuara et al., 2005; Chang et al., 2005; Huang et al., 2011, 2016). Mucosal ulceration and epithelial cell death (i.e., apoptosis, necroptosis, and necrosis) have been found in patients and animal models with inflammatory bowel disease (Heller et al., 2008; Qiu et al., 2011; Welz et al., 2011; Su et al., 2013; Pierdomenico et al., 2014). Various factors, such as inflammatory hypoxia, free radicals, immune factors (e.g., natural killer cells, cytotoxic T cells, and tumor necrosis factor α), or thermal stress as a physiological equivalent to fever, are all possible causes of induction of cell apoptosis and

necrosis (Kinoshita et al., 2002; Merger et al., 2002; Sun et al., 2002; Haynes et al., 2009; Sakiyama et al., 2009; Kallweit et al., 2012). With such a wide range of potential death stimuli, efficient cytoprotective mechanisms are crucial for the maintenance of epithelial survival and gut barrier integrity.

Rescue strategies against epithelial cell death by glucose

Protection against I/R injury by supplementation of glucose has been documented in various organs, including the kidney, heart and intestine (Kehrer et al., 1990; Ramasamy et al., 2001; Kozar et al., 2002). Glucose-mediated cytoprotection in gut epithelium has been reported after exposure to ischemic and inflammatory stress (Kozar et al., 2002; Huang et al., 2011, 2016). Enteral glucose not only prevents epithelial apoptosis and necroptosis but also restores crypt proliferative functions after ischemic insult (Huang et al., 2011, 2016). The attenuation of ischemic injury by glucose supplementation had previously been mistaken for an absence of stress stimuli. However, this hypothesis has recently been overturned by novel findings demonstrating that ischemia-induced cell death remains present despite replenishment of ATP (Huang et al., 2016). Here, the distinct cytoprotective roles of ATP, pyruvate, glucose metabolic enzymes, SGLT1-mediated signaling pathways, and the BAD/glucokinase axis will be highlighted (Fig. 1).

Roles of ATP

An energy decrease has been assumed to be the major cause of epithelial cell death under ischemia. In support of this hypothesis, numerous studies have shown that intestinal I/R-induced histopathological injury and barrier defects are alleviated by supplementation with enteral nutrients, such as glucose and glutamine (Ahdieh et al., 1998; Blikslager et al., 1999; Kozar et al., 2002; Sukhotnik et al., 2007). The beneficial effects of glucose and glutamine have been attributed to energy

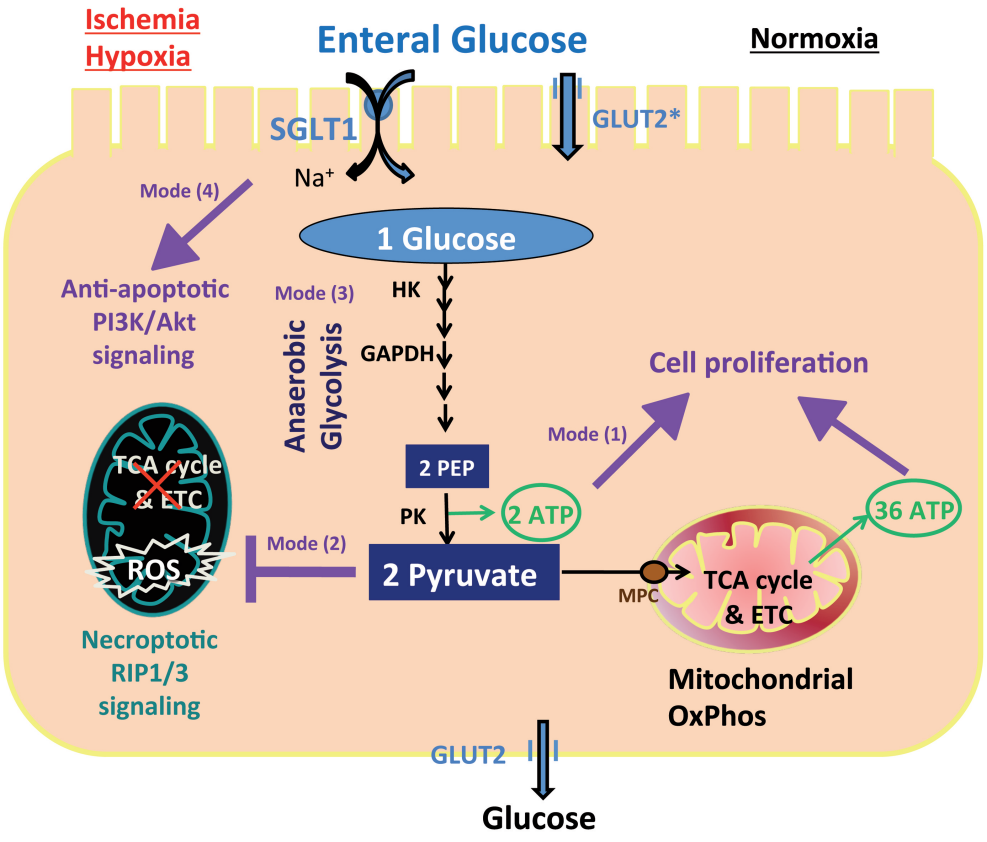

Fig. 1. Schema of glucose-mediated cytoprotection in intestinal epithelial cells under ischemic and hypoxic stress. Enterocytes constitutively express sodium-dependent glucose transporter 1 (SGLT1) on the apical membrane and glucose transporter 2 (GLUT2) on the basolateral membrane. After SGLT1 glucose binding, apical trafficking of GLUT2 (*) facilitates diffusion of enteral glucose. Glucose absorbed by enterocytes is either transported into the bloodstream to supply other viscera or undergoes anaerobic glycolytic metabolism and mitochondrial oxidative phosphorylation (OxPhos). One glucose is converted to two phosphoenolpyruvate (PEP) by the metabolic enzymes hexokinase (HK) and glyceraldehyde phosphate dehydrogenase (GAPDH) and subsequently is converted to two pyruvates and two ATPs by pyruvate kinase (PK). Pyruvate is then transported into the mitochondria by the mitochondrial pyruvate carrier (MPC) and enters the tricarboxylic acid cycle (TCA), which feeds into electron transport chain (ETC). The ETC then produces 36 ATP under normoxic conditions. Under ischemic or hypoxic conditions, massive cell death, including apoptosis and necroptosis, is triggered on villous epithelium; these effects are associated with a loss of crypt proliferation. The presence of enteral glucose protects ischemic gut epithelia through multiple modes of actions. Mode 1: Despite the lack of mitochondrial ATP synthesis under hypoxic conditions, glycolytic ATP increases crypt cell proliferation, thereby promoting epithelial restitution. However, ATP restoration does not prevent ischemic cell death. Mode 2: Glycolytic pyruvate inhibits receptor-interacting protein (RIP) 1/3-dependent necroptotic pathways via suppression of mitochondrial reactive oxygen species (ROS). Mode 3: Hypoxic adaptation induces transcriptional upregulation of HK, GAPDH and PK, thus increasing glycolytic pathways. Mode 4: SGLT1-mediated glucose uptake activates anti-apoptotic PI3K/Akt signaling pathways.

metabolism after sodium-dependent transporter uptake. Glutamine protection against I/R-induced epithelial barrier damage is also partly dependent on its role as an immune-enhancing agent (Kozar et al., 2004b; Sato et al., 2005). In contrast, alanine and arginine (as non-metabolizable solutes in the gut) cannot prevent ischemia-induced barrier damage (Kozar et al., 2004a,b; Sato et al., 2005). These results suggest that glucose and glutamine are preferable fuels for epithelial cells and confer protection against ischemic damage.

ATP is generally considered to be the predominant metabolite providing glucose protection in I/R damage. However, the exact modes and sites of action of ATP had not been elucidated until a recent study used liposomal delivery of ATP in place of enteral glucose. Enteral glucose has been found to prevent epithelial apoptosis and necroptosis and to restore crypt proliferation in the ischemic gut (Huang et al., 2011, 2016). However, replenishment of ATP also prevents crypt dysfunction but does not diminish the villous epithelial cell death or correct the histopathological damage in the ischemic intestine (Huang et al., 2016). These results are consistent with the hypothesis that ATP is crucial for active crypt proliferation and possibly for epithelial restitution and healing after blood reperfusion. Nevertheless, it challenges the traditional view that energy depletion is the initiating factor triggering epithelial cell death under ischemic stress and also suggests that an alternative metabolite might be responsible for the anti-death mechanisms.

Roles of pyruvate

Pyruvate is the end product of glycolytic metabolism. Under aerobic conditions, pyruvate is transported by the mitochondrial pyruvate carrier (MPC) and converted to acetyl-CoA, which enters into the tricarboxylic acid (TCA) cycle; this cycle produces nicotinamide adenine dinucleotide (NADH), which enters the electron transport chain (ETC) and results in ATP synthesis. In anaerobic conditions, pyruvate is reduced by NADH, thus forming lactate and the oxidized form of the co-factor NAD+. In addition to its metabolic role, pyruvate is also an endogenous scavenger for ROS, including superoxide and hydrogen peroxide (Brand and Hermfisse, 1997; Kao and Fink, 2010).

Abundant studies have shown that intraluminal or intravenous administration of pyruvate derivatives ameliorates free radical production and prevents intestinal I/R-induced mucosal injury and barrier damage (Cicalese et al., 1996; Cruz et al., 2011; Petrat et al., 2011). However, the source of free radicals, either from infiltrating phagocytes after blood reperfusion or from the stressed epithelia, has been unclear. To further investigate epithelial death, we have assessed the protective effect of pyruvate in intestines subjected to ischemic stress alone (Huang et al., 2016). Enteral instillation of pyruvate mimics the protective effect by glucose in terms of reduction of epithelial apoptosis and necroptosis but does not reverse the crypt dysfunction in the ischemic gut (Huang et al., 2016). These findings suggest that glucose-mediated epithelial cell death resistance is dependent on glycolytic pyruvate but not ATP (Huang et al., 2016). In addition to direct scavenging of free radicals, pyruvate also partially limits subsequent reperfusion injury by preventing epithelial death-dependent bacterial translocation and infiltration of phagocytes.

Roles of glucose metabolic enzymes

Under low-oxygen conditions in ischemia or inflammation, HIF-1 is translocated into the nuclei of intestinal epithelial cells (Koury et al., 2004). HIF-1 is a transcription factor that upregulates various glucose metabolic enzymes (Denko, 2008; Lu et al., 2008). A cytoprotective role of HIF-1 related to its transcriptional regulation has been documented in models of mesenteric ischemia and experimental colitis and in ileal loop models with exposure to bacterial toxins (Karhausen et al., 2004; Hart et al., 2011; Mones et al., 2011; Grenz et al., 2012; Keely et al., 2014). Moreover, HIF-1 activation is also linked to the resolution of intestinal ischemic injury as well as to adaptive protection by ischemic/hypoxic preconditioning (Koury et al., 2004; Chen et al., 2014). The glucose metabolic enzymes upregulated by HIF-1 include hexokinase (HK), glyceraldehyde phosphate dehydrogenase (GAPDH), and pyruvate dehydrogenase kinase (PDK) (Denko, 2008; Lu et al., 2008). However, most studies showing hypoxic adaptation for anaerobic glycolysis have been performed in colon adenocarcinoma cell lines (Denko, 2008; Lu et al., 2008; Marin-Hernandez et al., 2009). It therefore remains unclear whether findings in cancer cell lines can be translated to normal epithelium. Further studies on whether chronic or long-term HIF1-mediated glucose death resistance can drive genetic mutation and contribute to tumor transition from normal epithelium are needed. Metabolic reprogramming related to glycolytic enzymes in colon cancer, has been described in recent reviews (Marin-Hernandez et al., 2009; Semenza, 2010; Huang and Yu, 2015).

Roles of SGLT1-mediated signaling pathways

Several lines of evidence indicate that phosphatidylinositide 3-kinase (PI3K)/Akt and inhibitor of kappa b (IκB)/nuclear factor kappa b (NFκB) pathways are involved in non-nutritive mechanisms of SGLT1-mediated glucose cytoprotection. Previous studies have shown that SGLT1-dependent glucose uptake inhibits epithelial cell apoptosis caused by mesenteric I/R and microbial products, and activation of the PI3K/Akt pathways partly contributes to the anti-apoptosis response (Yu et al., 2005, 2006, 2008). Cotransport of sodium and glucose triggers the activation of Akt and results in recruitment of the

sodium-hydrogen exchanger to the apical membrane (Shiue et al., 2005), thus decreasing cellular acidosis. Others have demonstrated that SGLT1 activation by glucose or by non-metabolizable sugars suppresses proinflammatory NFκB signaling and IL-8 production in intestinal epithelial cells after endotoxemia (Palazzo et al., 2008). NFκB signaling has been linked to anti-apoptotic and pro-proliferative events in gastrointestinal epithelial cells (Potoka et al., 2000; Egan et al., 2004; Li et al., 2005; Liu et al., 2012).

Roles of glucokinase and pro-apoptotic regulator

An elegant study has demonstrated that glucose deprivation in hepatocytes results in cell apoptosis through a mechanism involving the dephosphorylation of BAD (a pro-apoptotic Bcl2 family member), which is associated with the suppression of glucokinase activity (Danial et al., 2003; Danial, 2008). Functionally similar to HK, which exists in all cell types, glucokinase is a glycolytic enzyme specific to hepatocytes and pancreatic β cells and acts in the first metabolic step, catalyzing glucose to D-glucose-6-phosphate. During cell apoptosis, oligomerization of BAK/BAD (in a dephosphorylated form) neutralizes the pro-survival Bcl-2, Bcl-XL, and Bcl-2 proteins and causes mitochondrial outer membrane permeabilization and cytochrome c release (Shimizu et al., 1999; Tsujimoto and Shimizu, 2000). BAD normally resides in a mitochondrial complex with glucokinase, and the phosphorylation of BAD is necessary for maximal glucokinase activity for glycolysis in hepatocytes (Danial et al., 2003).

The finding demonstrates that the BAD-glucokinase interaction is a key component of the glucose sensing machinery in normal hepatocytes. However, under cell death stimuli (e.g., glucose deprivation), dephosphorylated BAD coordinates the apoptotic and glycolytic pathways by simultaneously driving cell death and diminishing glucose utilization and metabolism (Danial et al., 2003; Gimenez-Cassina and Danial, 2015). Cells undergoing apoptosis also show decreased glycolytic ATP generation. This finding, together with our finding that restoration of ATP in the ischemic gut does not prevent epithelial apoptosis (Huang et al., 2016), suggests that an energy decrease may not be the initiating factor but instead may be a consequence of cell death. More importantly, the pro-proliferation ATP is not the major metabolite responsible for death resistance conferred by glucose in gut ischemia.

Concluding remarks

Novel findings challenge the traditional view of energy depletion as the major underlying cause of ischemic cell death and also argue against ATP being the principal protective glucose metabolite. The current understanding is that ATP is crucial for maintenance of crypt proliferation, whereas glycolytic pyruvate is the predominant metabolite for inhibition of villous epithelial death under ischemic stress. Overall, enteral glucose uptake (uncoupled with energy production) confers death resistance in ischemic epithelium, probably through multiple mechanisms that involve pyruvate-mediated free radical scavenging and SGLT1-mediated anti-apoptotic signaling.

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References

Ahdieh N., Blikslager A.T., Bhat B.G., Coleman R.A., Argenzio R.A. and Rhoads J.M. (1998). L-glutamine and transforming growth factor-alpha enhance recovery of monoacylglycerol acyltransferase and diacylglycerol acyltransferase activity in porcine postischemic ileum. Pediatr. Res. 43, 227-233.

Azuara D., Sola A., Hotter G., Calatayud L. and de Oca J. (2005). Apoptosis inhibition plays a greater role than necrosis inhibition in decreasing bacterial translocation in experimental intestinal transplantation. Surgery 137, 85-91.

Blikslager A.T., Rhoads J.M., Bristol D.G., Roberts M.C. and Argenzio R.A. (1999). Glutamine and transforming growth factor-alpha stimulate extracellular regulated kinases and enhance recovery of villous surface area in porcine ischemic-injured intestine. Surgery 125, 186-194.

Brand K.A. and Hermfisse U. (1997). Aerobic glycolysis by proliferating cells: A protective strategy against reactive oxygen species. FASEB J. 11, 388-395.

Chang J.X., Chen S., Ma L.P., Jiang L.Y., Chen J.W., Chang R.M., Wen L.Q., Wu W., Jiang Z.P. and Huang Z.T. (2005). Functional and morphological changes of the gut barrier during the restitution process after hemorrhagic shock. World J. Gastroenterol. 11, 5485-5491.

Chen Y., Lee S.H., Tsai Y.H. and Tseng S.H. (2014). Ischemic preconditioning increased the intestinal stem cell activities in the intestinal crypts in mice. J. Surg. Res. 187, 85-93.

Cicalese L., Lee K., Schraut W., Watkins S., Borle A. and Stanko R. (1996). Pyruvate prevents ischemia-reperfusion mucosal injury of rat small intestine. Am. J. Surg. 171, 97-100; discussion 100-101.

Cruz R.J. Jr, Harada T., Sasatomi E. and Fink M.P. (2011). Effects of ethyl pyruvate and other alpha-keto carboxylic acid derivatives in a rat model of multivisceral ischemia and reperfusion. J. Surg. Res. 165, 151-157.

Danial N.N. (2008). Bad: Undertaker by night, candyman by day. Oncogene 27 (Suppl 1), S53-S70.

Danial N.N., Gramm C.F., Scorrano L., Zhang C.Y., Krauss S., Ranger A.M., Datta S.R., Greenberg M.E., Licklider L.J., Lowell B.B., Gygi S.P. and Korsmeyer S.J. (2003). Bad and glucokinase reside in a mitochondrial complex that integrates glycolysis and apoptosis. Nature 424, 952-956.

Daniel H. and Zietek T. (2015). Taste and move: Glucose and peptide transporters in the gastrointestinal tract. Exp. Physiol. 100, 1441-1450.

Denko N.C. (2008). Hypoxia, HIF1 and glucose metabolism in the solid tumour. Nat. Rev. Cancer 8, 705-713.

Diamond J.M. and Karasov W.H. (1987). Adaptive regulation of

intestinal nutrient transporters. Proc. Natl. Acad. Sci. USA 84, 2242-2245.

Egan L.J., Eckmann L., Greten F.R., Chae S., Li Z.W., Myhre G.M., Robine S., Karin M. and Kagnoff M.F. (2004). Ikappab-kinasebeta-dependent nf-kappab activation provides radioprotection to the intestinal epithelium. Proc. Natl. Acad. Sci. USA 101, 2452-2457.

Ferraris R.P. and Diamond J. (1992). Crypt-villus site of glucose transporter induction by dietary carbohydrate in mouse intestine. Am. J. Physiol. 262, G1069-1073.

Ferraris R.P. and Diamond J. (1997). Regulation of intestinal sugar transport. Physiol. Rev. 77, 257-302.

Fleming S.E., Zambell K.L. and Fitch M.D. (1997). Glucose and glutamine provide similar proportions of energy to mucosal cells of rat small intestine. Am. J. Physiol. Gastrointestinal. Liver Physiol. 273, G968-G978.

Gimenez-Cassina A. and Danial N.N. (2015). Regulation of mitochondrial nutrient and energy metabolism by bcl-2 family proteins. Trends Endocrinol. Metab. 26, 165-175.

Godoy A., Ulloa V., Rodriguez F., Reinicke K., Yanez A.J., Garcia Mde L., Medina R.A., Carrasco M., Barberis S., Castro T., Martinez F., Koch X., Vera J.C., Poblete M.T., Figueroa C.D., Peruzzo B., Perez F. and Nualart F. (2006). Differential subcellular distribution of glucose transporters glut1-6 and glut9 in human cancer: Ultrastructural localization of glut1 and glut5 in breast tumor tissues. J. Cell. Physiol. 207, 614-627.

Grenz A., Clambey E. and Eltzschig H.K. (2012). Hypoxia signaling during intestinal ischemia and inflammation. Curr. Opin. Crit. Care 18, 178-185.

Guan Y., Watson A.J., Marchiando A.M., Bradford E., Shen L., Turner J.R. and Montrose M.H. (2011). Redistribution of the tight junction protein ZO-1 during physiological shedding of mouse intestinal epithelial cells. Am. J. Physiol. Cell. Physiol. 300, C1404-1414.

Gunther C., Neumann H., Neurath M.F. and Becker C. (2013). Apoptosis, necrosis and necroptosis: Cell death regulation in the intestinal epithelium. Gut 62, 1062-1071.

Hart M.L., Grenz A., Gorzolla I.C., Schittenhelm J., Dalton J.H. and Eltzschig H.K. (2011). Hypoxia-inducible factor-1alpha-dependent protection from intestinal ischemia/reperfusion injury involves ecto-5'-nucleotidase (cd73) and the a2b adenosine receptor. J. Immunol. 186, 4367-4374.

Hayashi M., Sakata M., Takeda T., Yamamoto T., Okamoto Y., Sawada K., Kimura A., Minekawa R., Tahara M., Tasaka K. and Murata Y. (2004). Induction of glucose transporter 1 expression through hypoxia-inducible factor 1alpha under hypoxic conditions in trophoblast-derived cells. J. Endocrinol. 183, 145-154.

Haynes T.E., Li P., Li X., Shimotori K., Sato H., Flynn N.E., Wang J., Knabe D.A. and Wu G. (2009). L-glutamine or L-alanyl-L-glutamine prevents oxidant- or endotoxin-induced death of neonatal enterocytes. Amino Acids 37, 131-142.

Heller F., Fromm A., Gitter A.H., Mankertz J. and Schulzke J.D. (2008). Epithelial apoptosis is a prominent feature of the epithelial barrier disturbance in intestinal inflammation: Effect of pro-inflammatory interleukin-13 on epithelial cell function. Mucosal. Immunol. 1 (Suppl 1), S58-S61.

Huang C.Y. and Yu L.C. (2015). Pathophysiological mechanisms of death resistance in colorectal carcinoma. World J. Gastroenterol. 21, 11777-11792.

Huang C.Y., Hsiao J.K., Lu Y.Z., Lee C.T. and Yu L.C.H. (2011). Anti-apoptotic pi3k/akt signaling by sodium/glucose transporter 1 reduces epithelial barrier damage and bacterial translocation in intestinal ischemia. Lab. Invest. 91 294-309.

Huang C.Y., Kuo W.T., Huang Y.C., Lee T.C. and Yu L.C. (2013). Resistance to hypoxia-induced necroptosis is conferred by glycolytic pyruvate scavenging of mitochondrial superoxide in colorectal cancer cells. Cell Death Dis. 4, e622.

Huang C.Y., Kuo W.T., Huang C.Y., Lee T.C., Chen C.T., Peng W.H., Lu K.S., Yang C.Y. and Yu L.C. (2016). Distinct cytoprotective roles of pyruvate and atp by glucose metabolism on epithelial necroptosis and crypt proliferation in ischemic gut. J. Physiol. (in press).

Jilling T., Simon D., Lu J., Meng F.J., Li D., Schy R., Thomson R.B., Soliman A., Arditi M. and Caplan M.S. (2006). The roles of bacteria and tlr4 in rat and murine models of necrotizing enterocolitis. J. Immunol. 177, 3273-3282.

Kallweit A.R., Baird C.H., Stutzman D.K. and Wischmeyer P.E. (2012). Glutamine prevents apoptosis in intestinal epithelial cells and induces differential protective pathways in heat and oxidant injury models. J. Parenter. Enteral Nutr. 36, 551-555.

Kao K.K. and Fink M.P. (2010). The biochemical basis for the anti-inflammatory and cytoprotective actions of ethyl pyruvate and related compounds. Biochem. Pharmacol. 80, 151-159.

Karhausen J., Furuta G.T., Tomaszewski J.E., Johnson R.S., Colgan S.P. and Haase V.H. (2004). Epithelial hypoxia-inducible factor-1 is protective in murine experimental colitis. J. Clin. Invest. 114, 1098-1106.

Keely S., Campbell E.L., Baird A.W., Hansbro P.M., Shalwitz R.A., Kotsakis A., McNamee E.N., Eltzschig H.K., Kominsky D.J. and Colgan S.P. (2014). Contribution of epithelial innate immunity to systemic protection afforded by prolyl hydroxylase inhibition in murine colitis. Mucosal Immunol. 7, 114-123.

Kehrer G., Blech M., Kallerhoff M., Kleinert H., Langheinrich M. and Bretschneider H.J. (1990). Glucose content and efficiency of glycolysis in protected ischemic kidneys of different species. J. Invest. Surg. 3, 147-168.

Kellett G.L. and Helliwell P.A. (2000). The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of glut2 to the brush-border membrane. Biochem. J. 350 Pt 1, 155-162.

Kight C.E. and Fleming S.E. (1995). Oxidation of glucose carbon entering the TCA cycle is reduced by glutamine in small intestine epithelial cells. Am. J. Physiol. Gastrointestinal. Liver Physiol. 268, G879-G888.

Kinoshita N., Hiroi T., Ohta N., Fukuyama S., Park E.J. and Kiyono H. (2002). Autocrine il-15 mediates intestinal epithelial cell death via the activation of neighboring intraepithelial nk cells. J. Immunol. 169, 6187-6192.

Kotler D.P., Levine G.M. and Shiau Y.F. (1980). Effects of nutrients, endogenous secretions, and fasting on in vitro glucose uptake. Am. J. Physiol. 238, G219-227.

Koury J., Deitch E.A., Homma H., Abungu B., Gangurde P., Condon M.R., Lu Q., Xu D.Z. and Feinman R. (2004). Persistent HIF-1alpha activation in gut ischemia/reperfusion injury: Potential role of bacteria and lipopolysaccharide. Shock 22, 270-277.

Kozar R.A., Schultz S.G., Hassoun H.T., DeSoignie R., Weisbrodt N.W., Haber M.M. and Moore F.A. (2002). The type of sodium-coupled solute modulates small bowel mucosal injury, transport function, and atp after ischemia/reperfusion injury in rats. Gastroenterology 123, 810-816.

Kozar R.A., Schultz S.G., Bick R.J., Poindexter B.J., DeSoignie R. and

Moore F.A. (2004a). Enteral glutamine but not alanine maintains small bowel barrier function after ischemia/reperfusion injury in rats. Shock 21, 433-437.

Kozar R.A., Verner-Cole E., Schultz S.G., Sato N., Bick R.J., DeSoignie R., Poindexter B.J. and Moore F.A. (2004b). The immune-enhancing enteral agents arginine and glutamine differentially modulate gut barrier function following mesenteric ischemia/reperfusion. J. Trauma. 57, 1150-1156.

Ley R.E., Peterson D.A. and Gordon J.I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 124, 837-848.

Li Q., Yu Y.Y., Zhu Z.G., Ji Y.B., Zhang Y., Liu B.Y., Chen X.H. and Lin Y.Z. (2005). Effect of nf-kappab constitutive activation on proliferation and apoptosis of gastric cancer cell lines. Eur. Surg. Res. 37, 105-110.

Linkermann A. and Green D.R. (2014). Necroptosis. N. Engl. J. Med. 370, 455-465.

Liu T., Liu D., Liu J., Song J.T., Gao S.L., Li H., Hu L.H. and Liu B.R. (2012). Effect of NF-kappab inhibitors on the chemotherapy-induced apoptosis of the colon cancer cell line ht-29. Exp. Ther. Med. 4, 716-722.

Lu C.W., Lin S.C., Chen K.F., Lai Y.Y. and Tsai S.J. (2008). Induction of pyruvate dehydrogenase kinase-3 by hypoxia-inducible factor-1 promotes metabolic switch and drug resistance. J. Biol. Chem. 283, 28106-28114.

Mace O.J., Morgan E.L., Affleck J.A., Lister N. and Kellett G.L. (2007). Calcium absorption by cav1.3 induces terminal web myosin ii phosphorylation and apical glut2 insertion in rat intestine. J. Physiol. 580, 605-616.

Madara J.L. (1990). Maintenance of the macromolecular barrier at cell extrusion sites in intestinal epithelium: Physiological rearrangement of tight junctions. J. Membr. Biol. 116, 177-184.

Marin-Hernandez A., Gallardo-Perez J.C., Ralph S.J., Rodriguez-Enriquez S. and Moreno-Sanchez R. (2009). HIF-1alpha modulates energy metabolism in cancer cells by inducing over-expression of specific glycolytic isoforms. Mini Rev. Med. Chem. 9, 1084-1101.

McElroy S.J., Underwood M.A. and Sherman M.P. (2013). Paneth cells and necrotizing enterocolitis: A novel hypothesis for disease pathogenesis. Neonatology 103, 10-20.

Merger M., Viney J.L., Borojevic R., Steele-Norwood D., Zhou P., Clark D.A., Riddell R., Maric R., Podack E.R. and Croitoru K. (2002). Defining the roles of perforin, fas/fasl, and tumour necrosis factor alpha in t cell induced mucosal damage in the mouse intestine. Gut 51, 155-163.

Mones R.L., Yankah A., Duelfer D., Bustami R. and Mercer G. (2011). Disaccharidase deficiency in pediatric patients with celiac disease and intact villi. Scand. J. Gastroenterol. 46, 1429-1434.

Moran A.W., Al-Rammahi M.A., Arora D.K., Batchelor D.J., Coulter E.A., Daly K., Ionescu C., Bravo D. and Shirazi-Beechey S.P. (2010). Expression of Na^+/glucose co-transporter 1 (sglt1) is enhanced by supplementation of the diet of weaning piglets with artificial sweeteners. Br. J. Nutr. 104, 637-646.

Ouiddir A., Planes C., Fernandes I., VanHesse A. and Clerici C. (1999). Hypoxia upregulates activity and expression of the glucose transporter glut1 in alveolar epithelial cells. Am. J. Respir. Cell Mol. Biol. 21, 710-718.

Palazzo M., Gariboldi S., Zanobbio L., Selleri S., Dusio G.F., Mauro V., Rossini A., Balsari A. and Rumio C. (2008). Sodium-dependent glucose transporter-1 as a novel immunological player in the intestinal mucosa. J. Immunol. 181, 3126-3136.

Petrat F., Ronn T. and de Groot H. (2011). Protection by pyruvate infusion in a rat model of severe intestinal ischemia-reperfusion injury. J. Surg. Res. 167, e93-e101.

Pierdomenico M., Negroni A., Stronati L., Vitali R., Prete E., Bertin J., Gough P.J., Aloi M. and Cucchiara S. (2014). Necroptosis is active in children with inflammatory bowel disease and contributes to heighten intestinal inflammation. Am. J. Gastroenterol. 109, 279-287.

Potoka D.A., Nadler E.P., Zhou X., Zhang X.R., Upperman J.S. and Ford H.R. (2000). Inhibition of nf-kappab by ikappab prevents cytokine-induced no production and promotes enterocyte apoptosis in vitro. Shock 14, 366-373.

Qiu W., Wu B., Wang X., Buchanan M.E., Regueiro M.D., Hartman D.J., Schoen R.E., Yu J. and Zhang L. (2011). Puma-mediated intestinal epithelial apoptosis contributes to ulcerative colitis in humans and mice. J. Clin. Invest. 121, 1722-1732.

Ramasamy R., Hwang Y.C., Whang J. and Bergmann S.R. (2001). Protection of ischemic hearts by high glucose is mediated, in part, by glut-4. Am. J. Physiol. Heart Circ. Physiol. 281, H290-H297.

Roediger W.E. (1982). Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterology 83, 424-429.

Sakiyama T., Musch M.W., Ropeleski M.J., Tsubouchi H. and Chang E.B. (2009). Glutamine increases autophagy under basal and stressed conditions in intestinal epithelial cells. Gastroenterology 136, 924-932.

Sato N., Moore F.A., Smith M.A., Zou L., Moore-Olufemi S., Schultz S.G. and Kozar R.A. (2005). Immune-enhancing enteral nutrients differentially modulate the early proinflammatory transcription factors mediating gut ischemia/reperfusion. J. Trauma 58, 455-461.

Semenza G.L. (2010). HIF-1: Upstream and downstream of cancer metabolism. Curr. Opin. Genet. Dev. 20, 51-56.

Shimizu S., Narita M. and Tsujimoto Y. (1999). Bcl-2 family proteins regulate the release of apoptogenic cytochrome c by the mitochondrial channel vdac. Nature 399, 483-487.

Shiue H., Musch M.W., Wang Y., Chang E.B. and Turner J.R. (2005). Akt2 phosphorylates ezrin to trigger nhe3 translocation and activation. J. Biol. Chem. 280, 1688-1695.

Sreenarasimhaiah J. (2005). Diagnosis and management of ischemic colitis. Curr. Gastroenterol. Rep 7, 421-426.

Stearns A.T., Balakrishnan A., Rhoads D.B. and Tavakkolizadeh A. (2010). Rapid upregulation of sodium-glucose transporter sglt1 in response to intestinal sweet taste stimulation. Ann. Surg. 251, 865-871.

Su L., Nalle S.C., Shen L., Turner E.S., Singh G., Breskin L.A., Khramtsova E.A., Khramtsova G., Tsai P.Y., Fu Y.X., Abraham C. and Turner J.R. (2013). Tnfr2 activates mlck-dependent tight junction dysregulation to cause apoptosis-mediated barrier loss and experimental colitis. Gastroenterology 145, 407-415.

Sukhotnik I., Khateeb K., Mogilner J.G., Helou H., Lurie M., Coran A.G. and Shiloni E. (2007). Dietary glutamine supplementation prevents mucosal injury and modulates intestinal epithelial restitution following ischemia-reperfusion injury in the rat. Dig. Dis. Sci. 52, 1497-1504.

Sun Z., Lasson A., Olanders K., Deng X. and Andersson R. (2002). Gut barrier permeability, reticuloendothelial system function and protease inhibitor levels following intestinal ischaemia and reperfusion--effects of pretreatment with n-acetyl-l-cysteine and indomethacin. Dig. Liver Dis. 34, 560-569.

Tsujimoto Y. and Shimizu S. (2000). Vdac regulation by the bcl-2 family of proteins. Cell Death Differ. 7, 1174-1181.

Vandenabeele P., Galluzzi L., Vanden B.T. and Kroemer G. (2010). Molecular mechanisms of necroptosis: An ordered cellular explosion. Nat. Rev. Mol. Cell Biol. 11, 700-714.

Welz P.S., Wullaert A., Vlantis K., Kondylis V., Fernandez-Majada V., Ermolaeva M., Kirsch P., Sterner-Kock A., van Loo G. and Pasparakis M. (2011). Fadd prevents RIP3-mediated epithelial cell necrosis and chronic intestinal inflammation. Nature 477, 330-334.

Wong J.M., de Souza R., Kendall C.W., Emam A. and Jenkins D.J. (2006). Colonic health: Fermentation and short chain fatty acids. J. Clin. Gastroenterol. 40, 235-243.

Yen T.H. and Wright N.A. (2006). The gastrointestinal tract stem cell niche. Stem Cell Rev. 2, 203-212.

Yu L.C.H. (2010). Protective mechanism against gut barrier dysfunction in mesenteric ischemia/reperfusion. Adapt. Med. 2, 11-22.

Yu L.C.H., Flynn A.N., Turner J.R. and Buret A.G. (2005). Sglt-1-mediated glucose uptake protects intestinal epithelial cells against lps-induced apoptosis and barrier defects: A novel cellular rescue mechanism? FASEB J. 19, 1822-1835.

Yu L.C.H., Turner J.R. and Buret A.G. (2006). LPS/CD14 activation triggers sglt-1-mediated glucose uptake and cell rescue in intestinal epithelial cells via early apoptotic signals upstream of caspase-3. Exp. Cell Res. 312, 3276-3286.

Yu L.C.H., Huang C.Y., Kuo W.T., Sayer H., Turner J.R. and Buret A.G. (2008). Sglt-1-mediated glucose uptake protects human intestinal epithelial cells against giardia duodenalis-induced apoptosis. Int. J. Parasitol. 38, 923-934.

Yu L.C.H., Wang J.T., Wei S.C. and Ni Y.H. (2012). Host-microbial interactions and regulation of intestinal epithelial barrier function: From physiology to pathology. World J. Gastrointest. Pathophysiol. 3, 27-43.

Zou X., Cao J., Yao Y., Liu W. and Chen L. (2009). Endoscopic findings and clinicopathologic characteristics of ischemic colitis: A report of 85 cases. Dig. Dis. Sci. 54, 2009-2015.

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